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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/596,479	03/29/2007	Bradley L. Urquhart	10935-35	7049

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EXAMINER	
THOMAS, TIMOTHY P	
ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
05/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/596,479	URQUHART ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *2 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-14* is/are rejected.

7)☒ Claim(s) *4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/3/2006; 8/16/2006; 3/27/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Acknowledgment is made of the preliminary amendment to the claims, filed 6/14/2006.

Election/Restrictions

2. Applicant's election without traverse of Group III in the reply filed on 2/25/2008 is acknowledged.

3. Applicant's election without traverse of Mesna as the Mesna or derivative compound specie, with the identification that claims 1 and 3-15 read on the compound; and specie (ii-c), Mesna in combination with another type of treatment for a disease associated with elevated plasma thiol levels, in the reply filed on 2/25/2008 is acknowledged.

4. Claims 2 and 15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2/25/2008.

Specification

5. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

6. The abstract of the disclosure is objected to because of the use of the legalese term, “comprising" in the 2nd line. Correction is required. See MPEP § 608.01(b).

Claim Objections

7. Claim 4 is objected to because of the following informalities: The claim ends with a comma instead of a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 14 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for dialysis treatment, in the sense of the meaning of amelioration of one or more symptoms or conditions or stabilization or the state of the disease, does not reasonably provide enablement for treatments in the sense of the meaning of preventing the disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Applicant has provided a special meaning to the term “treatment”, where beneficial or desired clinical results can include “preventing” spread of disease (specification, paragraph bridging pp. 7-8). This aspect of prevention is not considered enabled.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a method of lowering elevated plasma total homocysteine (tHcy) levels in a subject with end stage renal disease comprising admistering an effective amound of Mesna or a derivative thereof to a subject having end stage renal disease (ESRD); wherein the Mesna is administered in combination with other types of treatment for diseases associated with elevated plasma thiol levels. Thus, the claims taken together with the specification imply administration of Mesna to an individual with ESRD in combination with another type of treatment for diseases associated with elevated plasma thiol levels, such as dialysis, will prevent the spread of the ESRD.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Griffin, et al. ("Progression of Renal Disease: Renoprotective Specificity of Renin-Angiotensin System Blockade"; 2006; Clin. J. Am. Soc. Nephrol.; 1:1054-1065) teaches

that chronic kidney disease (CKD) tends to progress to ESRD, and studies of the underlying mechanisms of this progression have led to some understanding of mechanisms that contribute, although controversy persists about the relative pathogenic importance of the individual mechanisms (p. 1054, 1st paragraph); guidelines have been adopted for aggressive BP control, designed to slow the progression of nephropathies (p. 1054, 1st paragraph). This article has been cited to demonstrate that therapies are known that can slow progression of CKD to ESRD, but none are known that can prevent development of ESRD in CKD patients, implying that preventing disease spread in the more advanced ESRD would be even less predictable than preventing development of disease in CKD.

(5) The relative skill of those in the art:

The relative skill in the art is high.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for the reduction of homocysteine and cysteine levels in plasma and dialysate fluids upon administration of mesna coupled with dialysis.

However, the specification does not provide evidence or rationale that would support the claim to the prevention of the spread of ESRD, nor any other treatment besides dialysis used in combination with the administration of mesna that may potentially prevent ESRD spread.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to controversy among experts as to the importance of mechanisms of CKD development, the ability to reduce the progression of CKD to ESRD, but not prevention of this progression and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1, 3-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pendyala, et al. ("Intravenous Ifofamide/Mesna Is Associated with Depletion of Plasma Thiols without Depletion of Leukocyte Glutathione"; 2000; Clinical Cancer Research; 6(4): 1314-1321); and Cohen ("Methyl group deficiency and guanidine production in Uremia; 2003 Feb; Molecular and Cellular Biochemistry; 244(1-2): 31-36; cited in previous Office Action); in view of Wilcox (WO 01/30352 A1; 2001; IDS 8/3/2006 reference).

Pendyala teaches that mesna can reduce cystine and homocystine to cysteine and homocysteine, cysteine and homocysteine levels are inversely related to mesna levels, and the reduced forms are readily cleared by renal excretion (p. 1318, right, 3rd paragraph); administration of mesna (in combination with ifosamide) in a clinical trial produced a dose dependent depletion of total plasma cysteine and homocysteine in all patients, when administered by infusion (intraveneously) at 3-8 g/m^2/day (p. 1318, right, 2nd paragraph). Pendyala does not teach the administration of mesna to a patient with end stage renal disease or the combination of mesna administration with another treatment, such as dialysis or the specific dosage units and timing recited in claims 9-12. Cohen teaches that homocysteine, a substance known to produce vascular

damage, accumulates in subjects with uremia, such as in end-stage renal disease (abstract); treatments for uremia that have been used since the 1940's include dialysis (p. 31, left, 1st paragraph). Wilcox teaches a high t-Hcy plasma concentration resulting from hyperhomocysteinemia is considered a risk factor for artherosclerosis, occlusive vascular disease and coronary artery disease (p. 6, lines 13-15); folic acid (used to reduce t-Hcy concentration) is used in coronary artery disease resulting from hyperhomocysteinemia, arterial and venous occlusive diseases and has been studied in arthero- and thrombogenesis (p. 6, line 16 – p. 7, line 2; the implication is that reduction of homocysteine levels will reduce the risk of cardiovascular related diseases, such as artherosclerosis and veneous thrombosis). It would have been obvious to one of ordinary skill in the art at the time of the invention to administer mesna to a subject, including a human, with end-stage renal disease to lower the plasma homocysteine level and to combine this mesna administration with dialysis treatment, conducted during or after mesna administration. The motivation to administer mesna to a subject would have been the art recognized suitability for reduction of homocysteine in a subject with end stage renal disease; i.e., homocysteine, a compound that accumulates in patients with ESRD, is a toxin known to produces vascular damage; and therefore, the reduction of homocysteine plasma levels will reduce the risk of such damage. The motivation to combine mesna administration with dialysis would have been that the combination of mesa (suitable for cystine and homocysteine reduction in end stage renal disease patients) with the treatment of dialysis for end-stage renal disease would have been complementary treatments to 1) reduce cystine and homocystine to forms

more easily cleared by renal excretion in normally functioning kidneys and then 2) dialysis would have taken the place of the non-functioning kidneys in the patients with ESRD for removal of the toxic materials in the blood. It would have been obvious to optimize the dosage of mesna used, which would have given the dosages in the amounts and times recited in claims 9-12. The motivation would have been the routine optimization, considering that Pendyala teaches depletion of cysteine and homocysteine is dose-dependent. The risk reductions of the cardiovascular-related diseases, including artherosclerosis and veneous thrombosis would have been a natural outcome of the obviated combination therapy for lowering homocysteine levels in a patient.

Conclusion

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571)272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614